

DEPARTMENT OF VETERINARY PATHOLOGY, UNIVERSITY OF ZÜRICH

(DIRECTOR: PROF. DR. DR.H.C. H. STÜNZI)

RETAINED CARTILAGE IN THE ULNAR METAPHYSIS WITH DEFORMATION
OF THE FORELEGS IN TWO LITTERS OF CAPTIVE WOLVES

THESIS

PRESENTED TO THE
FACULTY OF VETERINARY MEDICINE, UNIVERSITY OF ZÜRICH
FOR THE
DEGREE OF DOCTOR OF VETERINARY MEDICINE

SUBMITTED BY

PETER OSSENT
MASE (VS)

REFeree: PROF. DR. DR.H.C. H. STÜNZI

REFeree: PROF. DR. P. SUTER

ZÜRICH 1982

ZENTRALSTELLE DER STUDENTENSCHAFT ZÜRICH

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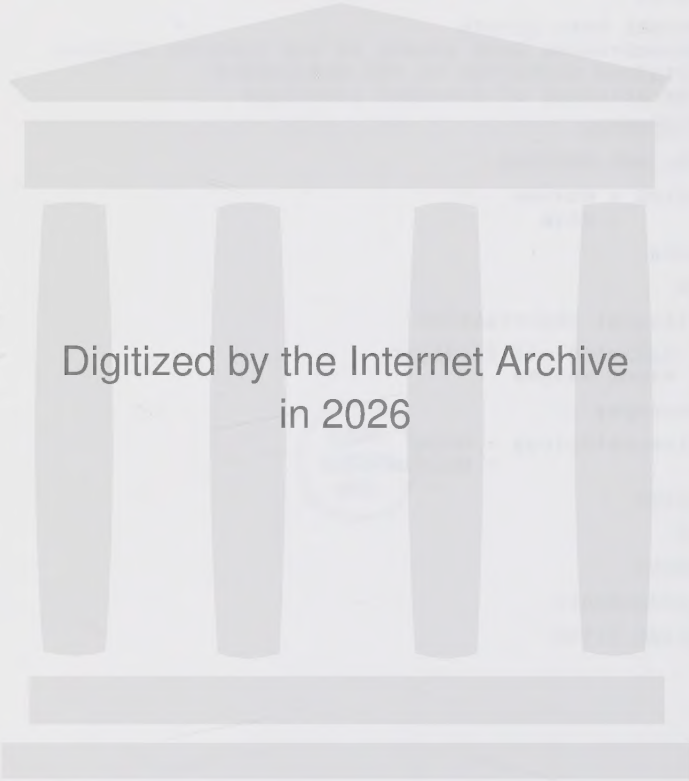
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INTRODUCTION

Asynchronous growth of the radius and ulna leading to a curvature of the foreleg is relatively common in dogs. It is the result of a premature cessation or retardation of growth, mostly in the distal ulnar growth plate (GP). Because of its unique shape and exceptional performance, this GP is especially prone to lesions which lead to growth disturbances and deformation of the bone.

In large and giant dogs bilateral bowing and angulation of the foreleg may be associated with a cone of retained cartilage extending from the GP into the metaphysis. The cause of this cartilage retention is not yet understood. Several factors or combinations of factors have been postulated, such as trauma, forced growth, deficiency in the blood supply, hormonal imbalance and hereditary or genetic defects.

A similar accumulation of cartilage occurs in the "leg weakness" syndrome on pigs, cattle, horses, turkeys and chickens and is regarded as a form of osteochondrosis.

In the Zürich zoo, bilateral lameness in the forelegs occurred in nine growing Mackenzie Valley forest wolves Canis lupus occidentalis, in two successive litters. In all animals the clinical and postmortem examination revealed, partly extensive, deformations of the forelimb and a persistence of large masses of cartilage in the distal ulnar metaphysis.

This seems to be the first observation of osteochondrosis in the GP of a non-domestic animal.

Because of the striking similarity between these changes and the ones reported in rapidly growing large dogs, a common etiology was presumed.

As a contribution towards the better understanding of such disturbances in general, the morphology of these lesions shall be described and the possible etiological factors shall be discussed based predominantly on the literature concerning dogs.

LITERATURE

a. Normal bone growth

The length of the long bones depends on the growth activity of the growth plates. These are the cartilage disks between epiphysis and diaphysis where bone growth takes place (Fig 1). Within the plate, chondrocytes lie in columns parallel to the long axis of the bone. From the epiphyseal to the diaphyseal side the cells are arranged in four merging zones; the resting, proliferating, maturing or hypertrophying and calcifying zones (Fig 3). A dense net of capillaries from the epiphyseal artery perforates the bone plate on the epiphyseal side of the GP. Solely these vessels are responsible for the viability and active anabolic processes in the plate. The cartilage itself is avascular but its boundaries are richly vascularized; a requirement dictated by the high metabolic rate associated with rapid cell proliferation and matrix synthesis.

The cartilage cells successively proliferate, mature and hypertrophy. In the last zone, at the juncture of the plate and the metaphysis, the matrix calcifies, the cells die and capillary loops of the medullary and metaphyseal vessels invade the ends of the columns. The horizontal matrix partitions between the now empty lacunae are resorbed, osteoblasts settle along the verticle remnants, deposit bone and form the first trabeculae, i.e. enchondral ossification takes place (12,45) (Fig 3).

The capillaries in the central metaphyseal area of the GP are terminal branches of the medullary arterial system. The outer ring of the GP is supplied by the metaphyseal arteries which anastomose with the peripheral medullary vessels (12,32,38) (Fig 2). Normal growth and bone formation depend on the integrity of the blood supply (48). The vessels on the metaphyseal side carry vitamin D, calcium and phosphates for the minerali-

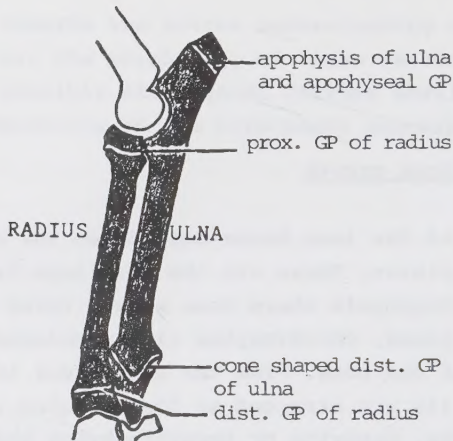


Fig 1

Drawing of the radius and ulna showing the position and shape of the growth plates (GP). Since the apophyseal plate of the ulna is proximal to the elbow joint, the distal ulnar GP and epiphysis must produce an equal length of bone as both of the radial growth areas combined.

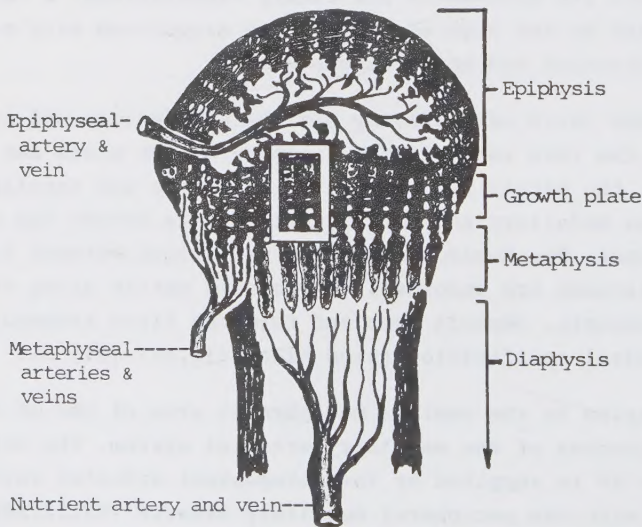


Fig 2

Drawing of the end of a growing bone and its different regions. The blood vessels necessary for the growth process are shown.

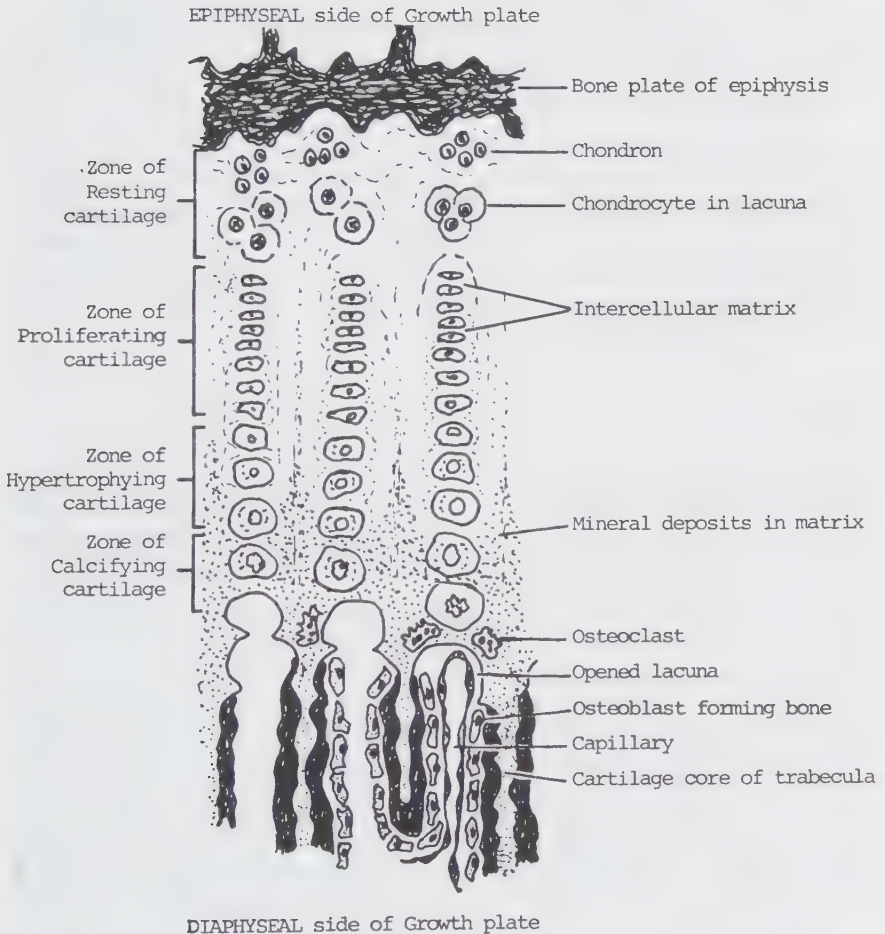


Fig 3

Drawing of the area indicated in Fig 2, showing the different zones of cartilage of the growth plate and how the cells and matrix develop before reaching the diaphyseal side.

zation of the matrix, they enable the removal of the degenerate cells and the deposition of lamellar bone. The blood has no nutritional importance for the chondrocytes - when this supply is severed experimentally the cells experience a new lease of life which suggests that the primary cause for their death is the presence of these vessels - with normal blood (49).

Special conditions exist in the foreleg (Fig 1) where the growth of the radius and ulna must be coordinated to guarantee proper alignment of the bones and normal articulation in the distal and proximal joints (7). These conditions are particularly delicate because of the considerable variation in the growth rate of the different plates.

The distal ulnar GP must produce 70% (15) to 85% (40) of the total ulnar length. The ulna is monoepiphyseal - the proximal growth area being an apophyseal plate which only serves the growth of the olecranon without contributing to the growth of the forearm. This means that the distal ulnar GP, together with the epiphyseal growth, must form an equal length of bone as the two radial GPs and their epiphyses combined (40,41). The performance required of this GP is thus the highest in the skeleton (23), and it is obvious that the disturbances at this site will be rapid with correspondingly grave consequences.

This high growth performance of the ulna is aided by two peculiarities which increase the surface area and sum of cartilage columns in the GP. Firstly, the flared metaphysis with up to 3 times the diameter of an adult bone and secondly, the GP's unique cone or funnel shape. The plate's conformation increases the surface area, over a disk of the same diameter, by 50% (40).

b. Asynchronous bone growth in the (canine) foreleg

The unique anatomical and physiological features make the distal ulnar GP especially vulnerable for mechanical injury and physiological imbalances. The subsequent growth disturbances, whatever the reason, may lead to a whole chain reaction, for the ulna will exert a bowstring effect on the normally developing radius. This causes the latter to curve away from its originally parallel partner. Bowing of the whole foreleg, carpal angulation, valgus, proximal subluxation of the ulna and distal subluxation of the radius, and osteoarthritis of the elbow and carpal joints may develop (1,4,7,20,21,22,28,31,40,43,54).

c. Retained cartilage in the metaphysis

The joint cartilage is the growth cartilage of the epiphysis. Should ossification not take place normally there will be a thickening of the cartilage. Degenerative changes in the basal layer, fissuring and finally erosion of the joint surface may follow. In the GP, proliferative processes on the epiphyseal side must harmonize with the resorption of cartilage on the metaphyseal side. Here, as in the joint cartilage, any inhibition of ossification will rapidly lead to the build-up of excess cartilage. The term osteochondrosis is used for this condition, regardless of whether it involves the joint or the growth cartilage. In chickens and turkeys dyschondroplasia is the usual designation for the condition within the metaphysis (16,19,23,25).

The phylogenetically closest animal to the wolf, the dog, frequently has retained cartilage in the distal ulnar metaphysis during the phase of maximal growth. These wedge shaped accumulations of hypertrophic chondrocytes may be several centimeters long and reach from the GP far up into the metaphysis (4,6,20,51). The cones are usually bilateral (22,28,31,40,46,54). They may occur in the distal femur and proximal tibia as well (23).

The majority of descriptions are based on radiological findings where radiolucent cones may be seen extending from the GP. Their shape and size varies considerably and their outlines are described as being either irregular or smooth. With progressing growth of the bones these structures were seen to disappear or to lie further up in the shaft (31).

In rapidly growing pigs, retained cartilage was described at the GPs of the ulna, femur, humerus, ribs, and vertebrae (35). In fattening bulls similar accumulations were seen in the metacarpus, metatarsus and distal radius and ulna (36). Also in broilers and turkeys the proximal tibia and tarso-metatarsus were affected (29,30).

d. The etiology of retained cartilage

The retention of cartilage in the ulna of dogs has been regarded a sequel of ischemia in the mid-metaphyseal region caused primarily by a deficiency in the blood supply from the nutritive artery (40). Qualitative and quantitative deviations from the normal would slow down enchondral ossification and lead to the accumulation of cartilage. The periphery of the GP was assumed to lie too far from the core for the anastomoses from the metaphyseal arteries (38) to have a compensatory function. This was the explanation for the predominantly central location of the retained cartilage cones.

Injury occurs relatively easily in the GPs of the forelimbs of giant dogs, especially when they are in the phase of maximal growth. A seemingly minor insult such as jumping down from a higher level may be sufficient to cause such damage, for the GPs are the weakest links in the series of bones and ligaments of the limb (21,42). The consequences depend on the type of injury inflicted and the zone affected. Impaction or separation along or across the GP may occur (32). Damage from the former will usually be located on the epiphyseal side of the plate and may

cause an interruption of its nutrient blood supply. Chondrogenesis and therefore bone growth will be retarded or even cease and may lead to GP closure (22). Shearing forces may lead to epiphyseal separations in the hypertrophied cartilage zone which, being the weakest layer, is a potential cleavage line (5). Chondrogenesis continues normally whilst the resorption of cartilage and enchondral ossification suffer extensive hinderances on the diaphyseal side of the plate. An accumulation and retention of cartilage result (7,20,21). This type of injury, however, will be a sequel to a single insult and is more likely to be one sided.

Chronic trauma from the excessive body weight on the immature limb may similarly lead to disturbances in the medullary blood supply. It was postulated that microcompressions inflicted over longer periods may result in microemboli which in turn would compromise the circulation at the site of enchondral ossification. The consequent hinderances would lead to an accumulation of cartilage (22,40).

In all three forms of injury, ulnar growth is retarded and may cause the complications arising from asymmetrical growth mentioned before.

GPs in general and the distal ulnar GP in particular are not only mechanically weak but also physiologically unstable. Giant dogs and food animals bred and managed for maximal performance will have less compensatory reserves should any imbalances occur than for instance smaller, slower growing animals (25,40).

Qualitative and quantitative aspects of nutritional factors come into consideration. Imbalances may lead to an array of metabolic disturbances in which metaphyseal bulging, carpal angulation and thickening of the GPs is seen (8,13,14,28,46,51,54). Changes in the calcium-phosphorous ratio and deficient vitamin D intake or resorption were thought to cause osteochondrosis in large dogs (27). Excessive mineral uptake, especially calcium, was thought to act via calcitonin to cause similar lessions (14).

Again it was speculated that nutritionally accelerated growth will precipitate or aggravate such disturbances if a certain genetic predisposition is present (1,6,23,46).

Hormonal imbalances are frequently held responsible for disturbances in the mechanisms of enchondral ossification (3,16,26,46). The selection for size as in animals with high growth performance seems to be related to high levels of somatotropin (17). In the pig multiple osteochondritic skeletal defects have been regarded as effects of an endocrinopathy (44).

An unspecific hereditary tendency for maldevelopment may be a further potential cause (9,46). Although retained cartilage can affect whole litters of dogs (23), a study of 200 Great Danes allowed no connection to be established between osteochondrosis and hereditary factors (27). Also extensive studies have been carried out with pigs. The question has not been answered conclusively here either (19). Descriptions of the histopathological appearances associated with retained cartilage and features of the affected GPs do not seem to exist for the dog. On the other hand, much work has been done on pigs, where the "leg-weakness" syndrome is of great economic importance (2,3,10,35, 47). The histological lesions occurring in intensely fed cattle (36), horses (37), turkeys (29) and chickens (30) have also been described.

CASE HISTORIES

In the colony of Mackenzie Valley timber wolves, Canis lupus occidentalis, in the Zürich zoo, two successive litters developed deformations of the forelegs in two consecutive years. In the 4 survivors of the first litter the deformities were observed at the age of 3-4 months, whereas the 5 littermates of the following year showed the first changes already at the age of two months.

The same parents had produced a total of 5 puppies in the 2 years prior to the birth of the animals described here. Two died when a few days old, the remaining three were sold at the age of 11 months without any deformities being noted.

The father was caught in the wild in Canada and the mother was his daughter by a canadian wild female from another province. The mother was born and raised in Zürich.

The wolves were kept in an earthen floored enclosure of 30x25 m. It has 2 levels, one 6 m above the other with a steep bank of earth and rock in between. The animals were always very active and spent a good part of the day walking or trotting up or down the incline.

From the age of approx. 3 months onwards, the puppies took increasingly larger quantities of meat directly, i.e. no longer from their parents. At 4 months the average daily ration, for they were fed together, was 2 - 2 1/2 kg of beef or horsemeat per animal. Occasionally they were given whole rabbits, chickens, rats, guinea pigs and apples and pears. The second litter received cottage cheese and a sprinkling of the rations with a mineral and vitamin supplement. (Vionate^R, Squibb/Opopharma Zürich).

MATERIAL & METHODS

MATERIAL

WOLVES: The four wolves from the first litter were killed when approx. 8 months old (Fig 4). The bone deformities by this stage had progressed so far that this became unavoidable. Once it was realized that the second litter was developing the same disturbances it was decided to investigate the problem systematically.

Thus, starting at the age of approx. 3 months the first pup of the second litter was euthanatized. The others were euthanatized at 35 day intervals to follow the progression of the lesions. Although very difficult to judge in the unrestrained animals, the wolf with the most marked distension of the carpus was usually chosen. The oldest animal was killed at the age of 8 months.

All offspring examined were females but for the third and fifth animals of the second litter.

The parents were also euthanatized and included in the investigation since it was decided not to breed with them any longer.

Dogs: Bone and cartilage samples from 10 dogs of breeds, size and age comparable with the wolves and which had shown no signs of bone disease, were collected from routine necropsy material. Histological sections were made from the same regions as of the wolves and used as comparative material.

METHODS

The clinical findings in the wolves were recorded and the forelimbs were radiographed. Complete hemograms were obtained and blood chemistry values, including serum calcium and phosphorous

levels, were determined. A complete necropsy was performed. The organ and bone samples were fixed for histopathology in 4% buffered formol, paraffin embedded and 6 μ sections made and stained in the routine way with haematoxylin-eosin (H-E). The bones were sawed in several parallel approx. 7 mm thick slices (38) and decalcified in 10% formic acid after fixing.

The combined Alcian blue - Periodic-acid-Schiff-reaction (AB-PAS) was additionally used on bone sections. Some samples of retained cartilage were sectioned without prior decalcification and stained by the method of Kossa.

RESULTS

a. Clinical observations

In both litters the first abnormalities were noticed between 2-4 months of age. Some animals showed intermittent lameness and buckling at the carpus while descending the incline when the maximum weight was borne by the forehand. In all of the animals progressive distension and cranial bowing of the lower leg became apparent concurrently to the rapid increase in weight and size (Fig 1). Slight lateral angulation of the foot was evident in a few animals. The degree of lameness increased with the severity of the deformity (Fig 5). None of the wolves showed anything pathological apart from the foreleg deformity.

The mother of the wolves was in good physical condition except for an intermittent foreleg lameness. At the age of 16 years the father of the wolves was emaciated and was reluctant to move in the last few months prior to his being euthanatized.

Radiological findings:

All wolves - apart from the father - had a moderate to high degree of radial curvature and usually a curvature of the ulna as well. The heavily distended ulnar metaphyses of the growing animals contained a radiolucent core of varying size and shape (Fig 6). In some animals the radiocarpal joint had developed a valgus deformity. The remaining structures were normal.

Blood values:

The hemograms and blood chemistry were normal when compared with the values for the dog.

b. Necropsy

The body weights, crown-rump measurements and their increase with age are shown in Fig 4.

The forearm deformity in all wolves was always bilateral but the curvature of the radius and ulna usually was asymmetrical (Fig 8). Higher degrees of asymmetry and change generally were seen in the first litter in which all were of the same age when necropsied. The ulnar metaphysis was up to 4,5 cm wide and the length of the right and left ulnae differed up to 4 cm. The distension of the distal ulnar metaphysis observed in all animals explains the carpal swelling (Fig 5).

The ulna was consistently reduced in length when compared to the radius. There was a varying degree of radial curvature. Mainly the distal half of the bone was wrapped around the epiphysis of the ulna so that the articular surface was rotated 90° in a volar direction. Thus in several animals the joint surface came to lie parallel to the longitudinal axis of the radius (Fig 7). The ulna was less curved than the radius. Each contained large masses of cartilage in the metaphysis.

The shape of the retained cartilaginous areas varied considerably (Figs 9-14). Partly they were tongue-shaped and long, partly squat blocks completely filling the metaphysis. Some were broken up into islands or contained greenish sequesters of bone and seemingly degenerating tissue. Others extended several centimeters diagonally across the metaphysis and into the cortex of the diaphysis causing localized necrotic-looking bony defects which were visible through the periosteum (Fig 7). Still others formed plugs completely separated from the normal GP by several centimeters of normal spongiosa or by a narrow connecting bridge in between. Some of the bones had a second, newer cone-shaped mass of cartilage accumulating at the GP next to older remnants further up in the metaphysis (Fig 11).

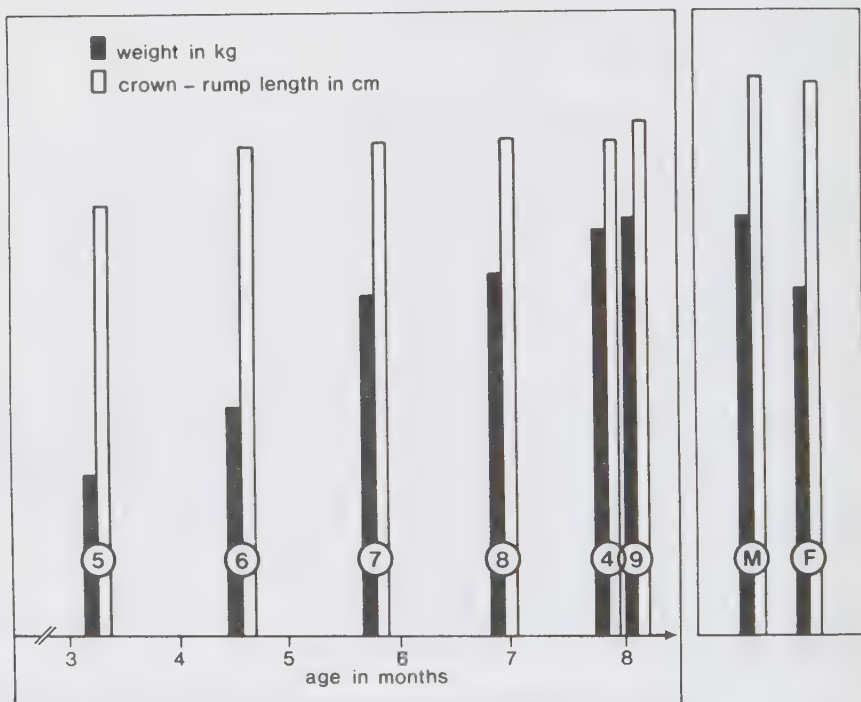


Fig 4

Graph illustrating data obtained from wolves 4-9 at necropsy. Each double column represents one animal. On the right, as a comparison, are the values for the mother and father. Wolves 7 & 9 were males.

Note the near linear increase of weight with age and how the puppies attained the near size of their parents at the early age of 4-5 months.

Usually, the cut surface of the retained cartilage was firm, striated longitudinally and had a wavy transverse pattern. When teased, the columns easily separated into strands. Older cartilage remnants appeared whitish, structureless and chalky. The edges of the retained cartilage varied from smooth to rough. The latter form, which predominated, appeared to contain more chalky material. The periphery of the GP, between the cone and the cortex, was mostly still visible in its normal thickness (Fig 17). The epiphysis, bony diaphysis and the ulnar articular cartilages were unaltered.

In the other bones only the GPs of the radius, tibia and femur were slightly altered. The spectrum of these changes varied from mere irregularities in GP thickness and progressed to the formation of small spicules of firm, clear cartilage of several millimeters length. The more cartilage that was retained in the ulna, the more irregular were the GPs of the other bones. The extreme was in the 4 1/2-month-old wolf number 6, where the distal femur and distal tibia possessed 4 mm wide, tapered, whitish and amorphous cartilage stripes. Some of these extended from the GP vertically across the metaphysis and into the cortex which at this point also had a whitish colour. The bases of the cartilaginous tongues lay in the acute angles formed by the GPs which meant there were 2 parallel stripes in each bone (Figs 15 & 16).

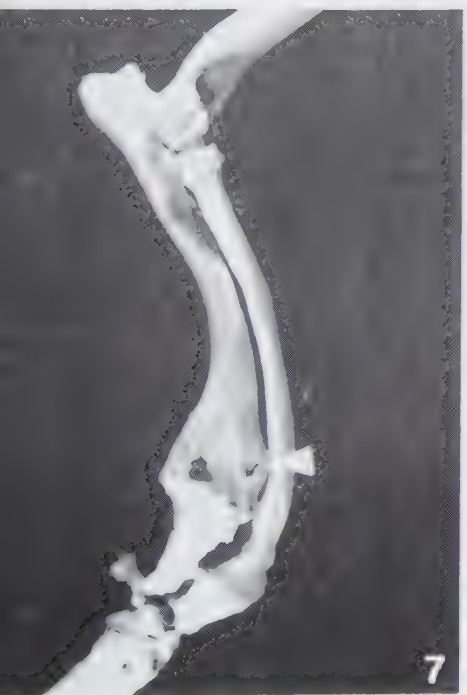
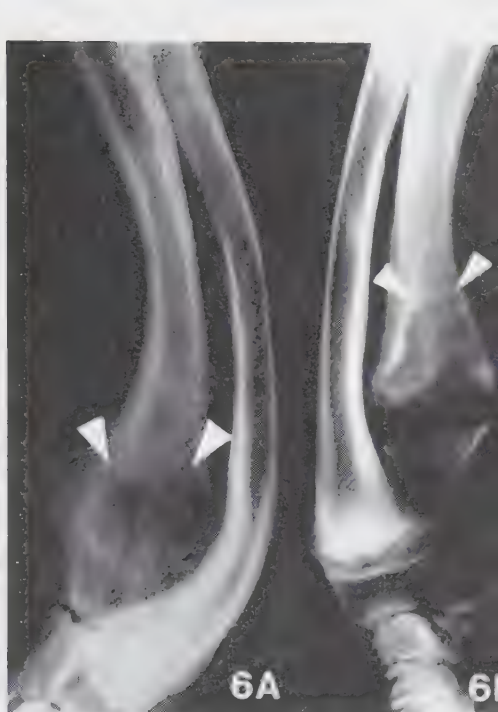
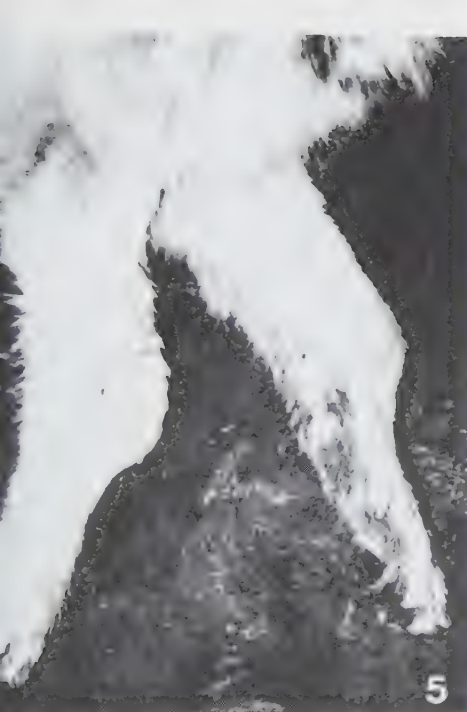
The second litter of 5 animals, killed at 35 day intervals, showed clear differences from animal to animal. The amount of retained cartilage increased from the first to the second wolf and then successively decreased in the older 3 animals. The 3-month-old wolf (No 5) possessed a small centrally located cone in the right ulna (Fig 9), a smaller dome in the left ulna and spicules in both distal radial GPs. The 4 1/2-month-old wolf (No 6), the most seriously affected of all 9 animals, had cartilage remnants in both ulnae with a width of 4 cm and a length of 6 cm which practically filled the metaphysis from cortex to cortex (Fig 10). Wolves 7,8 and 9 which were euthan-

Fig 5 Detail of forelegs showing the heavily distended carpal areas (Wolf 4, 8 mo).

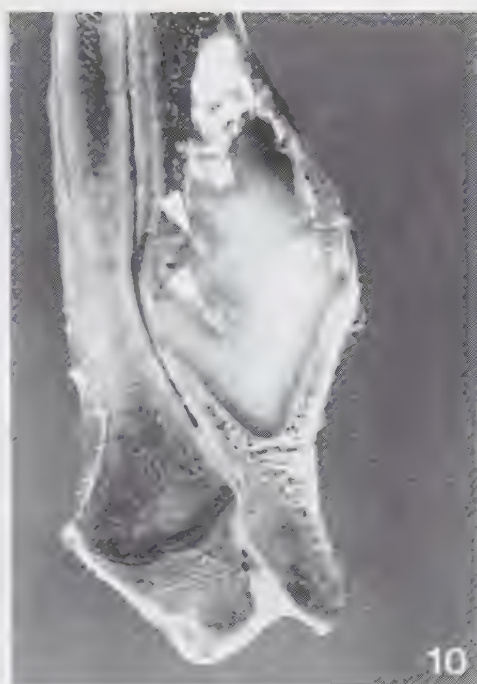
Fig 6 Radiographs of the distal radius and ulna of (A) Wolf 4, 8 mo, (also in Figs 5 & 7) and (B) Wolf 6, 4 1/2 mo, (also in Fig 10). The arrows indicate the outlines of a large mass of retained cartilage extending from the ulnar GP into the metaphysis.

Fig 7 Macerated right radius and ulna (same animal as in Figs 5 and 6A). Note the curvature of the radius around the distended metaphysis of the ulna; the 90° deviation of the carpal articular surface which is now parallel to the vertical axis of the limb; the ulnar metaphysis with localized porous structure where retained cartilage interfered with the formation of the cortex (arrow).

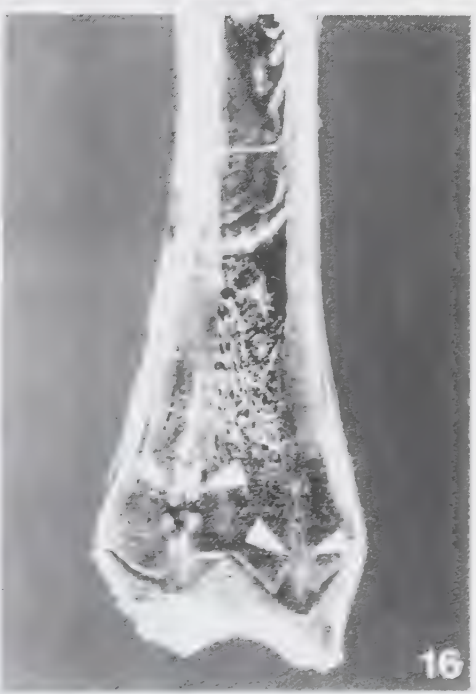
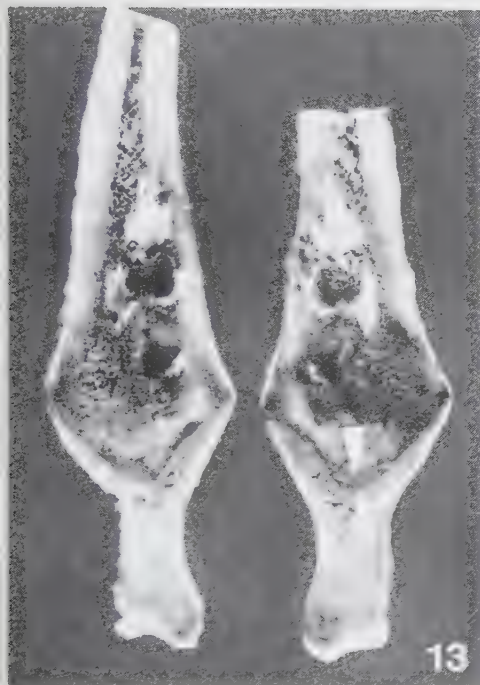
Fig 8 Lateral view of radius and ulna of 2 littermates. (left: Wolf 2, right: Wolf 1, both 8 mo.) Obvious is the varying degree of bone curvature, distension of the ulnar metaphysis and deviation of the carpal joint surface.



- Fig 9 Small cone of retained cartilage adjacent to the distal ulna GP. (Wolf 5, 3 mo.) Edges rough and white. Peripheral GP regions of normal thickness. Radius with small spicule of cartilage (arrows).
- Fig 10 Massive retention of cartilage extending from cortex to cortex. (Wolf 6, 4 1/2 mo., same animal as in Fig 6B). Cartilage is striated in the longitudinal axis. The oldest proximal remnants are white and amorphous. Cortex also affected. Small islands of bone being formed within the cartilage (arrows).
- Fig 11 Island of retained cartilage extending from the ulnar metaphysis into the diaphysis. (Wolf 1, 8 mo.) Newer cone of cartilage accumulating at the GP.
- Fig 12 Large retained cartilage plug connected to the normal GP by a narrow bridge. (Wolf 3, 8 mo.) Normal spongiosa in between.



- Fig 13 Cartilage remnants irregularly interspersed in the bone of the ulnar metaphysis. (Wolf 9, 8 mo.) GP also irregular in thickness (arrows).
- Fig 14 Ulnar GP closed. (Wolf 2, 8 mo.) Massive plug of retained cartilage in the metaphysis extending from cortex to cortex.
- Fig 15 Distal femur. (Wolf 6, 4 1/2 mo.) Cone shaped cartilage remnants in one of the angles of the GP with a long streak of cartilage extending several centimeters into the metaphysis and cortex.
- Fig 16 Distal tibia. (Wolf 6, 4 1/2 mo.) Cones and streaks of retained cartilage in both angles of the GP extending far into the spongiosa of the metaphysis (arrows).



atized at 5 1/2, 7 and 8 months respectively, were obviously recovering from worse stages (Fig 11-13). Wolf 7 had smaller cones in both ulnae (Fig 11) and spicules of up to 8 mm in one distal radius. An unusual finding was an older callus in the right ulna of wolf No 8 approx. 6,5 cm above the GP. In the spongiosa there were older cartilage islands at the same level, which had definitely weakened the bone. The GPs of both ulnae of wolf No 9 were merely irregular in thickness (Fig 13).

The last wolf, killed at the age of 8 months, (No 9) had nearly normal spongiosa but several very irregularly shaped islands of cartilage and bone in the metaphysis. The GPs varied only slightly in thickness. There was no pronounced bowing of the forelegs.

The mother's forearms were asymmetrically curved but not as severely as those of her offspring. The metaphyses were normal.

Examination of the hip and shoulder joints of the father revealed bilateral chronic arthrosis with extensive erosion, fissuring and brown discolouration of the articular surfaces. The forearm bones were absolutely straight and showed no residues of abnormality in the metaphyseal spongiosa. Additionally, chronic interstitial nephritis was diagnosed; alterations frequently seen in canines of his age.

The inner organs of all animals - in particular the endocrine glands - revealed no alterations.

c. Histopathology

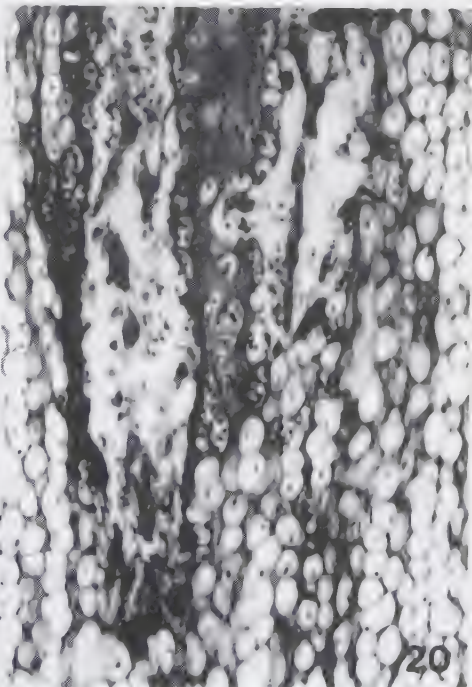
Dogs:

The thickness of the distal ulnar GPs was approx. 0,8 mm; whereby the general thickness diminished with age. The apex of the GP often contained a small cartilage dome in the acute angle. The thickness of the radial GP was remarkably constant in all animals. The GPs of most dogs contained several eosinophilic streaks per section; some even bridging the whole GP. Often these coincided with a larger vessel in the epiphyseal bone plate. Other features were small spikes of up to 2 mm length protruding from the plate, a disorientation of the chondrocyte columns and a zig-zag deformation of portions of the plate with the vertical sections of the zig-zag narrowed down to 0,1 mm. Small, approx. 4 and 6 mm long smooth-edged cones of hypertrophied cartilage were seen in the distal ulna of 2 of the 10 dogs.

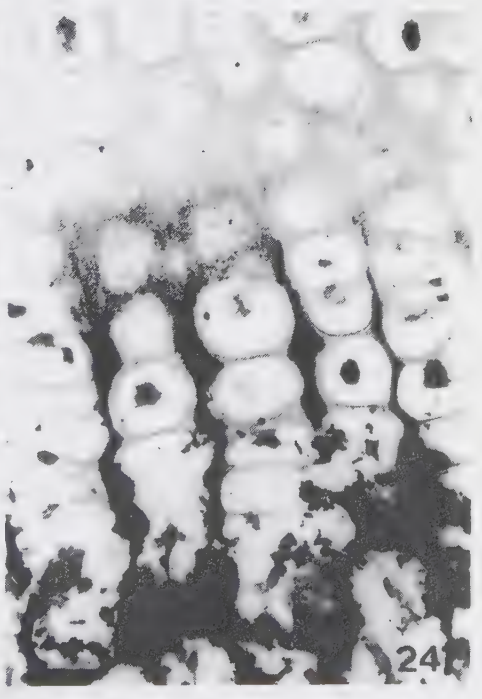
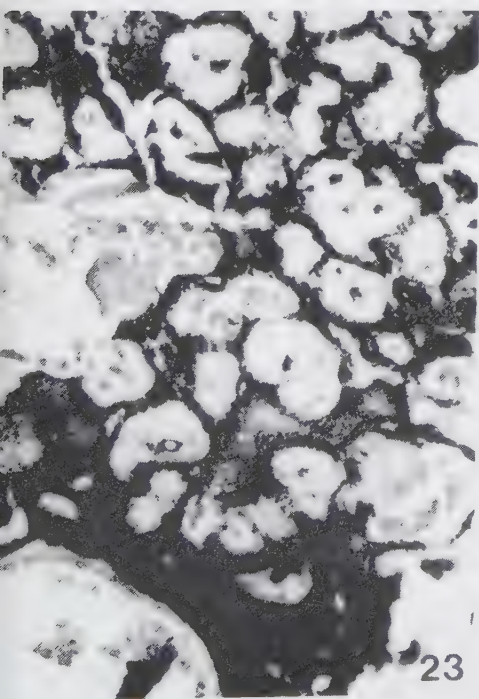
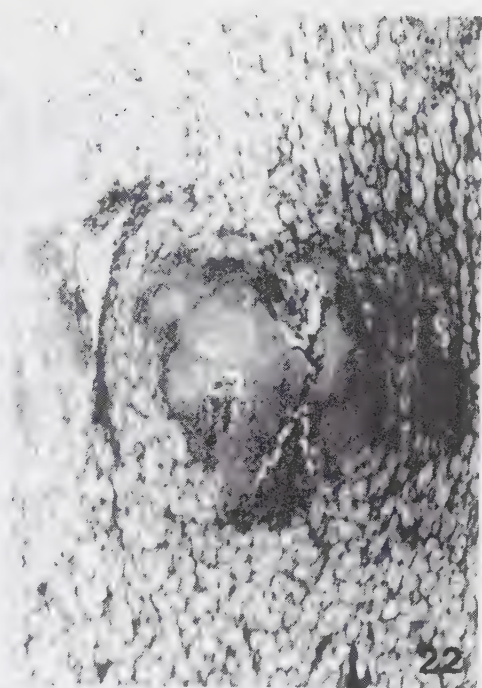
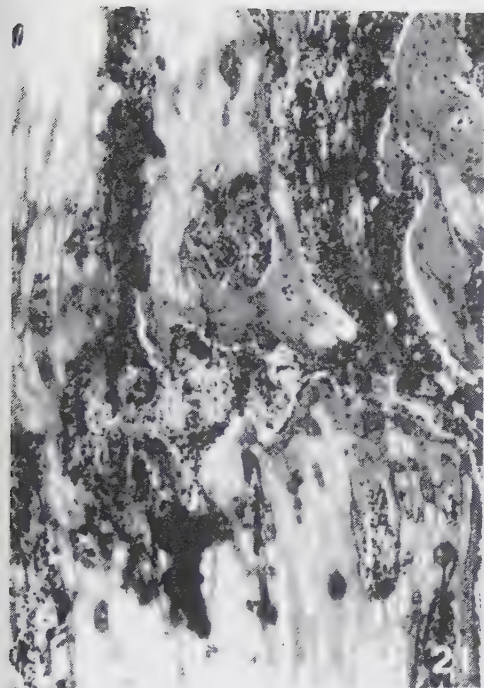
Wolves:

Histological examination of the grossly normal parts of the ulnar GPs next to the cones revealed very similar but more pronounced alterations than the corresponding GPs of the dogs. The thickness of the still open GPs were practically the same. Wolves 2 and 4 had closed GPs and large islands of retained cartilage further up in the metaphyses (Fig 14). These two animals had the extremities with the most pronounced bowing and left-right asymmetry. The first 3 zones of chondrocytes in the GPs under the cones were always normal (Fig 17). The accumulated cartilage consisted solely of hypertrophied cells of which the matrix was only mineralized in the narrow region close to the edges (Fig 23) as opposed to the cartilage in the normal GP where only the matrix of the last few cell layers is mineralized (Fig 24). There was a considerable variation in the staining of the intercellular matrix. With AB-PAS (and H-E) all shades were

- Fig 17 Distal ulna (Wolf 3, 8 mo; H-E, x 40). Normal GP with different zones of cartilage on the lower right. In the centre normally developing bone trabeculae. On the left the edge and base of a cone of hypertrophic cartilage.
- Fig 18 Distal radius (Wolf 6, 4 1/2 mo; H-E, x 40). Edge of a larger spicule protruding from the GP into the metaphysis. Normal ossification, smooth junction of cartilage to bone.
- Fig 19 Distal ulna (Wolf 3, 8 mo; H-E, x 40). Detail of distal end of a retained cartilage island. Active ossification, numerous osteoclasts, irregular new bone trabeculae and ossification front. Faintly staining cartilage.
- Fig 20 Higher magnification (x 100) of cartilage island shown in Fig 19. Notice the gossamer like appearance of the matrix and the minute cell remnants.



- Fig 21 Distal ulna (Wolf 2, 8 mo; H-E, x 40). Lateral edge of retained cartilage island with invading vessels and osteoclasts. Active ossification on all fronts.
- Fig 22 Distal ulna (Wolf 2, 8 mo; H-E, x 40). New bone island deep within retained cartilage. Several blood vessels are present in the periphery of the bone.
- Fig 23 Distal ulna (Wolf 2, 8 mo; undecalcified section, Kossa, x 250). Edge of retained cartilage cone. The mineralization of the matrix extends relatively far from the site of ossification. Black structures at bottom are bone trabeculae.
- Fig. 24 Normal GP of a dog (undecalcified section, Kossa, x 250) showing the same border of cartilage to bone as in Fig 23. Mineralization extends only 3 cell-layers into the cartilage.



to be seen varying from pale pink in the old, thin-walled cartilage with sparse matrix and small shrunken nuclei (Fig 20), to a deep blue (or basophilia with H-E) in the young tissue where the cell cytoplasm was mostly still visible (Fig 17). The weakly staining cartilage remnants which had seemed chalky and white at gross examination, had not disintegrated but had retained a gossamer like appearance (Figs 19 & 20). Practically all retained cartilage, even when located several centimeters from the GP, was still arranged in recognizable columns. The borders of cartilage to bone were being ossified most actively, the cones on the sides and proximal ends and the cartilage islands at the distal ends as well (Figs 17-21). The smaller cones had better delineated edges with a regular transition to the primary spongiosa (Fig 18).

However, the proximal edges of the larger cones and particularly the circumference of the islands, i.e. the older cartilage, had very irregular edges. This was caused by columns, still several cell rows thick, protruding into the spongiosa (Fig 20). In the cartilage islands the blood vessels seemed to break into the columns easier from the ends (Fig 20) than from the sides (Fig 21). Often in the older remnants, vessels had made their way far into the cartilage masses and ossification had proceeded from the inside forming bone islands from within (Fig 22).

The articular cartilage of the ulna was normal. The bone trabeculae and the cellular components also were normal, as was the bone of the epiphysis and the cortex. The only bone structures directly influenced by the retained cartilage were localized areas in the metaphyseal cortex of wolves 2,4 and 6. Here the cones were so shaped that they had interfered with the normal formation of cortical bone. The trabeculae were thin and incomplete with little osteoid. On gross examination these areas had been judged to be necrotic. In the macerated bone the surface and cortex was spongy (Fig 7).

The microscopic examination of the radius, femur and tibia confirmed the gross findings. The histological structure of the GPs was far more disorganized but of the same type as that of the dogs used as a comparison. The costochondral junction was sporadically and very slightly disorganized but there was no accumulation of excess cartilage.

DISCUSSION

Morphological changes

There was ample evidence for a connection between retained cartilage in the distal ulnar metaphysis and retarded growth at this site. Ten wolves, i.e. all apart from the father, had varying degrees of bowing of the forelegs. Some wolves had only mild deformations whilst others could barely walk. The distension of the carpus was far more pronounced than in a normally growing puppy of comparable size.

In all the growing animals the foreleg deformity was associated with retained cartilage in the ulnar metaphysis. The shape, exact location and size of the accumulations varied considerably from one animal to the next and, to a lesser extent, from one side to the other. In the first litter of four 8-month-old animals the bowing of the forelegs was severe and the cartilage often filled the whole metaphysis from cortex to cortex. In the second litter the 4 1/2-month-old wolf had similarly pronounced accumulations of cartilage. The next animal was not so severely affected and the two older animals showed obvious signs of repair with disintegration and ossification of the cartilage masses; a situation which ultimately may well have reverted to near normal given enough time. The bowing of the last two animals was not so pronounced as to have been a serious hinderance to moving around.

There were obvious signs that there had been alternating periods of poor and normal ossification. This was evident in the bones which had large islands of retained cartilage within the metaphyses and a second cone shaped mass of cartilage forming on the GP separated from the island by normal spongiosa. Three wolves had retained cartilage only in the form of islands. Repair was nearing completion.

One wolf with the most developed cartilage remnants in the ulna was found to have long narrow bilateral tongues of cartilage extending from the GPs into the metaphyses of the distal tibia and distal femur. The shape of these bones, however, was normal. Most animals had spicules and irregularities of thickness in the distal GP of the radius.

Histologically the retained cartilage was shown to be still viable and noncalcified apart from the last thin layer next to the zone of ossification. As opposed to normal GP cartilage, which is supplied by the epiphyseal vessels (12), the retained cartilage, especially that of the islands, must have its nutrient supply taken over by the medullary vascular system. The rough-edged cartilaginous areas were interspersed with particularly irregular new bony trabeculae; the older the cartilage remnants the more irregular their edges.

Comparison with other animals

Cartilage spicules, irregularities and "eosinophilic streaks" are frequent occurrences in the GPs of young pigs (3,47) and in our samples taken from routinely necropsied growing dogs. The question where the border to the pathological lies has not been settled. It is likely though that the metaphyses of all animals with a forced growth performance are affected with such slight morphological changes. The "eosinophilic streaks" in piglet GP cartilage consisted ultrastructurally of narrow zones of altered matrix and were assumed to be traces of atrophied blood vessels (2).

Retained metaphyseal cartilage, i.e. lesions similar to those seen in the wolves, are known to occur spontaneously in various species of domestic animals and are considered to be a manifestation of osteochondrosis (9,19,23,25). Food producing animals and large dogs - all with high demands on the growth performance - are typically affected. The primarily altered tissues are the GP-cartilages of the long bones - those responsible for

the high performance. The articular cartilage may be affected by a similar thickening and the lesions may occur at both sites simultaneously (24).

Early reports on retained metaphyseal cartilage cones in the dog only mention the one localization - the distal ulna (28,40). The occurrence of such cartilage remnants in multiple skeletal locations in the pig and bull (35,36) suggested that the condition should also have a multiple manifestation in the canine. In later reports multiple lesions were described in dogs (23,24) and now in wolves. In all cases the changes occurred first in the distal ulna.

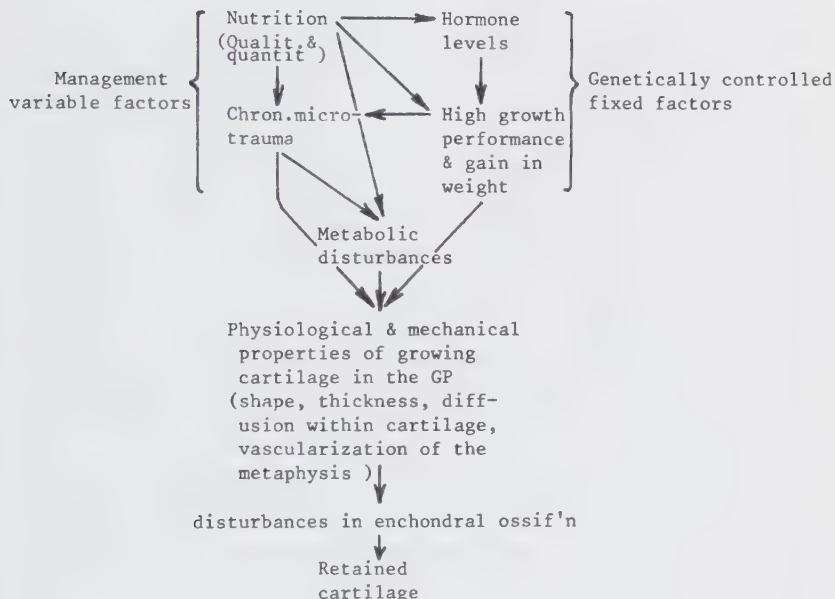
Retained cartilage in otherwise normal long bones can easily be distinguished clinically, radiographically and histologically from the metabolically induced, generalized bone growth diseases summarized "epiphyseal osteopathies" (8). Included in this group are conditions such as rickets, scurvy, Möller Barlow, hypertrophic osteodystrophy and osteodystrophy II (8,13,14,28,46,51, 54). Neither radiographically nor morphologically did the wolves show any indication of metabolic bone growth disturbances.

Causes for deficient ossification

In either case, the hypothetical causes for the articular or the GP form of osteochondrosis are manifold and incompletely understood. They seem to be the same for both abnormalities. Retained cartilage is thought to result from an imbalance between the proliferative and the resorptive processes in the enchondral ossification at the edge of the cartilage. The balance is in favour of proliferation and thus cartilage accumulates. What happens morphologically is plainly visible but an explanation of the causes for these morphological changes is not so clear.

Generally, the factors which may participate in the pathogenesis of retained cartilage in the metaphysis may be divided into two groups (see diagram p. 35). There are constant factors which

are genetically fixed features in the animal and there are variable factors which are under the external influences of management. Some factors are equally effected from both sides.



The interactions of the two groups and of the individual factors are most intricate, however, for the variables in the pathogenesis are numerous and the combinations of etiological factors even more so. Nearly all factors influence one another to some extent. e.g. The growth rate may be fixed genetically on the one hand and strongly influenced by feeding on the other hand. Nutrition may modify factors as diverse as the rate of growth and weight increase, the thickness of the GPs or the level of serum hormones. The high potential for growth, raised to the utmost by one sided management, renders the GPs vulnerable to even slight degrees of stress or minor traumatic insults. Obviously the sum

of negative influences must attain a threshold value before they have any adverse effect. In the wolves several of the above factors were present and others were assumed to have been or could not be excluded.

At first, the possibility of a hereditary problem in the wolves seemed likely because of the inbreeding. The mother with a slight foreleg deformity produced nine offspring with similar deformities of varying severity when inbred to her father. All the wolves were raised in the same enclosure. The same subspecies has been kept under identical conditions in the Zürich zoo for the past 17 years, without any mention of bone deformations in the records. Nevertheless, one apparent exception was discovered by coincidence. The forelegs of the skeleton of an adult wolf, from the same zoo, in the collection of the veterinary anatomical department, Zürich, were very obviously curved - more so than those of the mother of our two litters. Unfortunately, no medical information was available on this animal but it was possible to exclude a familial relationship between that animal and the group described here. This and the fact that the father of our two litters and the mother's mother were both caught in the wild in different canadian provinces make the probability of direct hereditary influences seem less likely.

In the large, fast growing dog breeds an increase of 50 - 100 times the body weight in the first 6-8 months is possible (27, 40). Wolves are also very rapidly growing animals having nearly attained the full body size by the age of about half a year (18). Domestic animals are selected for an exceptionally high growth rate either for economic reasons in food producing animals or for aesthetic or functional purposes in dogs (24,25,40). These extremes in weight gain and growth can only be achieved in conjunction with a correspondingly rich diet. The direct connection between calorific intake, rapid growth and osteochondrosis was clearly demonstrated experimentally for pigs (34), fattening bulls (36), broilers (30) and turkeys (29). A similar predisposition for bone growth disturbances, and osteochondrosis, has

been assumed for giant dogs (6,23). Further supporting evidence for the above is that a successful therapeutic measure for dogs suffering from such disturbances is a change in the diet with a reduction in the intake of proteins and energy in general (1,19, 40). This alone may be sufficient to give the ossification process enough time to catch up. Varying the concentrations of these substances may induce changes in the composition and amounts of growth factors. This was shown in experiments designed to study the connections between over-nutrition and skeletal disease in growing Great Danes (14). The excessive intake of proteins, calories and minerals accelerated growth and led to a deficient cartilage maturation in the GPs. This led to cell enlargement with displacement and narrowing of the cartilage matrix septa and a widespread retardation of bone resorption in metaphyseal trabeculae. The mechanism was thought to be induced by hypercalcemia resulting in hypercalcitonism and hypoparathyroidism. Unfortunately, changes in the distal ulnar GPs were not described but the changes for instance in the chondrocostal junction resemble closely those observed in the metaphyses of the wolves. There is no doubt that the wolves received a more than adequate diet.

A vitamin or direct mineral imbalance in the wolves was not regarded as likely. Nevertheless, the classical disturbances of bone metabolism and growth (13) had to be considered and excluded. The regulatory hormones participating in the processes, however, are much more likely to have been involved. For instance, calcitonin is important for the maturation process of cartilage and is directly influenced by nutritive calcium uptake. Growth hormone or somatotropin (STH) has an anabolic effect and via its mediator somatomedin also influences the growth of long bones (33). The mitotic rate in the chondrocytes and matrix production are enhanced. The thickness of the GP increases (45). Pigs selected for rapid growth and meat production have higher serum STH- and somatomedin-levels than pigs of the slower growing breeds (39). Furthermore, it is of interest to note that a higher incidence and severity of osteochondrosis was observed in pigs selected for fast growth and less fat as opposed to pigs

selected for slow growth and more fat (11). In dogs as well, it is likely that the selection for 'giant' body size is a selection of animals with elevated levels of STH (17). The Canadian wolves are without doubt fast growing animals - an adaptation imposed by the harsh environmental conditions (18). Factors of natural selection will favour animals with a high growth rate, and maybe raised STH-levels. It is well known that growing dogs of large breeds are much more liable to suffer from osteochondrosis than dogs of small breeds (6,24). In humans, increased alimentary protein uptake and increased amino acid concentrations in the plasma may lead to elevated serum STH-levels (33). The food rations of the wolves consisted of exceptionally large quantities of meat daily from the age of 3-4 months onwards. A connection does not seem too far fetched; a genetically fixed potential for forced growth performance, coupled with an additional nutritionally induced elevation of STH may well be an unfortunate combination in the pathogenesis of retained cartilage in the wolves. The endocrine balance in all animals suffering from osteochondrosis seems to be worth close scrutiny and may well prove to be a rewarding field for further research.

Predisposing systemic factors are modified by local factors such as the shape, location, composition and load bearing on the GP. These local factors may be responsible for deficient cartilage ossification. The GPs in the three most vulnerable sites - the distal ulna, femur and tibia - have an unusual shape, possessing either one or two adjacent angles when the bone is sectioned lengthwise (52). The thickness of the cartilage of these GPs varies markedly; especially the tips of the angles are considerably thicker and may even form small cartilage domes. An increased incidence of osteochondrosis in dogs has been observed in the cartilages with the highest growth performance. These GPs normally remain relatively thick for the first 4-5 months (23). The increase of lesions may be explained by the fact that the additional cell layers, especially in the angles, serve as a barrier to diffusion or increase the distance which must be bridged by essential substances e.g. hormones, minerals and proteins.

Cartilage maturation may be delayed by an imbalance, deficiency or a total lack of these vital factors. Wolves, being closely related to dogs may experience similar diffusion hinderances.

On the molecular level possible explanations for delay or failure in enchondral ossification are disturbances in the composition and of the mechanical properties of cartilage. Aberrations in the complex biochemical properties of the cartilage tissue have been observed and regarded as causes of articular osteochondrosis in pigs (2); i.e. not only are the mechanical properties of osteochondritic cartilage altered but probably its metabolism as well. Normally maturing growth cartilage chondrocytes become larger, accumulate glycogen, produce alkaline phosphatase and become increasingly calcified. They then degenerate, die and the spaces are then invaded by capillaries and osteogenic cells from the diaphysis (12). Biochemical investigations were not possible in conjunction with the wolves. Alterations in this respect cannot be excluded.

Another predisposing factor which may lead to failures in ossification - also on the molecular level - are adverse qualitative or quantitative changes in the medullary vascular supply to the GPs (40). Adequate volume, oxygen tension and pressure are necessary for the calcification and for the penetration of vessels into the matrix. Support for this hypothesis can be obtained from experiments on rabbits (5,49,50,53) where interference with the blood supply to the GPs of the tibia or radius produced identical metaphyseal cones as seen in spontaneous GP-osteochondrosis. The changes within the bones of the wolves match well with the experimentally induced cartilage accumulations. The matrix of the hypertrophied cells in the rabbits was also not calcified (49). The GPs with an exceptionally high growth performance, in particular the distal ulnar GP, depend on a correspondingly well developed blood supply (23). In the dog, the nutrient artery was considered to be prone to disturbances since it enters the bone at an angle and at a considerable distance from the GP (40). Perfusion experiments in turkeys with retained cartilage failed to reveal abnormalities of vasculature in the bones (29).

A direct connection between the hinderances in the vascular supply and chronic micro-trauma has been assumed in dogs (22, 40). We never observed any histological changes to support this theory. Nevertheless, the mechanical stresses on the limbs of the growing wolves must have been exceptionally high for the ulnar GP and probably for the GPs of the hind legs too. The steep incline in their enclosure certainly intensified the effect. The topography of the enclosure is probably a feature unique to the Zürich zoo.

The mechanisms discussed partially explain the pathogenesis of the failures in enchondral ossification of the wolves. Several questions nevertheless remain unanswered. Some variable must have newly appeared in this group of animals. Large numbers of wolves have been kept in the same enclosure in the Zürich zoo for many years without any complications arising. Thus it seems likely that the variable may have been a genetic factor after all.

SUMMARY

Two litters comprising nine wolves (Canis lupus occidentalis) from the zoological garden, Zürich, developed bilateral distension of the carpus and cranial bowing of the foreleg beginning at the age of 2 months. The animals were born in 2 consecutive years and had the same parents.

The first litter of 4 was killed without diagnosis. The pups of the second litter were killed at regular intervals to enable the study of the different stages of the condition. The cause for the disturbances was revealed to be retained cartilage at the distal ulnar growth plate. These cartilage masses were in all animals, bilateral and in different stages of development or regression. The resulting retardation of ulnar growth and the asynchronous development of the parallel bones of the foreleg led to their deformation, to positional changes in the carpus and to lameness.

The pathogenesis of the build up of cartilage was attributed to a lack of enchondral ossification on the diaphyseal side of the growth plate (GP) although cell proliferation on the epiphyseal side of the plate was normal. The condition belongs to the osteochondrosis complex.

Many causes for this discrepancy between growth and resorption have been postulated for various species of domestic animals with similar lesions. There is mostly circumstantial and partly experimental evidence that disturbances in the medullary blood supply, which in these cases could have been caused by chronic micro-trauma, may be a triggering and aggravating mechanism. The ulnar GP is a region which is close to the point of physiological imbalance anyway; a result of the forced performance imposed on such rapidly growing, relatively heavy animals. The causes probably involve a combination of hormonal, genetic, metabolic and

nutritional factors. The changes will appear first in the GPs which must meet the highest demands on growth performance. The opinion that imbalanced STH-levels cause such disturbances in pigs led us to postulate that this hormone also must execute a key function in the pathogenesis of retained cartilage in the wolves.

In genetically and nutritionally forced dogs and food animals retained cartilage may be avoided by reducing food and protein intake and by preventing chronic injury to the GPs.

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